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COAGULATION DEFECTS IN GLOMERULONEPHRITIS AND THE NEPHROTIC SYNDROME

By

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Blood coagulation was studied in 70 cases of acute, in 4 of subacute, in 34 of chronic glomerulonephritis and in 20 of nephrotic syndrome; 780 coagulation studies involving 16 different procedures were carried out. Close attention was given to the clinical course.

Hypercoagulability was invariably demonstrable at the onset of typical acute, and during acute exacerbations of chronic glomerulonephritis. The signs were more marked in the nephrotic syndrome whether of the primary type or secondary to amyloidosis, diabetic glomerulosclerosis or systemic lupus erythematosus. A case of Goodpasture's syndrome was likewise associated with hypercoagulability though an antithrombin factor of heparin character was demonstrated just before death. Hypocoagulability was most frequent in inactive chronic glomerulonephritis. On the other hand, hypercoagulability may be interpreted as a sign of activity in nephropathies, and its persistence is an adverse prognostic sign.

Anticoagulants failed to produce any decisive change in 8 patients with glomerulonephritis or the nephrotic syndrome.

Production of fibrin clots in the glomerular loops in human glomerulonephritis, occasionally even in large numbers (Reichel-type) has long been noted by pathologists, and it has also been demonstrated in the glomerular lesions of rats [19] and dogs [24] treated with nephrotoxic serum. We have presented indirect evidence of coagulation defects in nephrotoxin-treated rabbits. In the successive stages of the process, gelatin-stabilized India-ink was injected intravenously according to JANCSÓ. On treatment with very potent nephrotoxin, India-ink thrombi plugging the small vessels were demonstrable in the renal cortex. Precipitation of the exogenous colloid was interpreted as a sign of latent coagulopathy [11, 12, 13]. On the grounds of these findings, we have now studied the coagulation defects associated with glomerulonephritis and the nephrotic syndrome. Our first results were reported in 1967 [4]. The question has been investigated simultaneously by numerous other authors and various coagulation defects were described [1, 5—8, 10, 16, 18, 20—23, 25].

The present work was carried out to study the relationship between coagulation defects and the clinical course of renal disease.

Material and methods

In 128 patients, 780 coagulation studies were performed. Of the patients, 70 had acute, 4 subacute and 34 chronic glomerulonephritis and 20 were nephrotic. The following 16 laboratory tests were performed.

1) Bleeding time, according to DUKE;
2) Whole blood clotting time, according to LEE and WHITE;
3) Platelet count by phase contrast microscopy, according to BRECHER and CRONKITE;
4) Clot retraction, according to BIGGS and MCFARLANE;
5) Coagulation time of recalcified plasma, according to HOWELL;
6) QUICK's prothrombin time;
7) Prothrombin consumption;
8) Study of serum coagulation accelerating factor, according to HORN, KOVÁCS and ALTMANN;
9) Thrombin time;
10) Thrombin clotting time in the presence of toluidine blue (Toluidine blue time);
11) Thrombin inactivation time, according to GERENDÁS;
12) Fibrinogen gravimetry;
13) Euglobulin lysis time, according to VON KAULLA and SCHULTZ;
14) Partial thromboplastin time;
15) Thromboplastin generation test, according to BIGGS and DOUGLAS;
16) Thromboelastography according to HARTERT.

We primarily relied on the plasma fibrinogen level, euglobulin lysis time and on thromboelastography (TEG). The hatched areas seen in the diagrams correspond to the scatter of the normal values. The normal thromboelastogram is represented by a broken line. Maximum elasticity of thrombus (mε) has also been represented. Measurement of partial thromboplastin time and the thromboplastin generation test were confined to cases involving particular problems. The coagulation tests were supplemented with capillary tests (LANDIS, GÖTHLIN, RUMPEL-LEEDE, BORBÉLY).

The dynamics of the process responsible for the primary disease was checked on the grounds of several parameters, as seen in the diagrams. The most important of these included the Addis count [26], estimation of protein excretion by measurement of the amount of nitrogen, serum albumin, the serum complement titre [17], ASO-titre, GFR measured by routine endogenous creatinine clearance. In special cases, the clearance of inulin and PAH and the filtration fraction were also estimated.

Results

Fig. 1 summarizing the results shows that a normal coagulation was confined to a fraction of the patients, mostly after the cure of glomerulonephritis. The predominant coagulation defect in the various types of glomerulonephritis and nephrosis was a hypercoagulability, either isolated or together with signs of hypocoagulability. It is therefore the relationship between hypercoagulability and the clinical course which had first to be considered.

In the early stage of typical acute glomerulonephritis hypercoagulability was a regular finding. An illustrative case is given in the following.

The patient was a 19-year-old female, first seen on the 17th day of acute glomerulonephritis. The high fibrinogen level, the protracted euglobulin lysis time and the broad thromboelastogram were conclusive of hypercoagulability. Penicillin treatment resulted in an improvement of the condition, with the disappearance of gross haematuria, reduction in the Addis count of erythrocytes and in hypercoagulability. Even microscopic haematuria diminished to a minimum, and this could be considered a residual haematuria, the more so

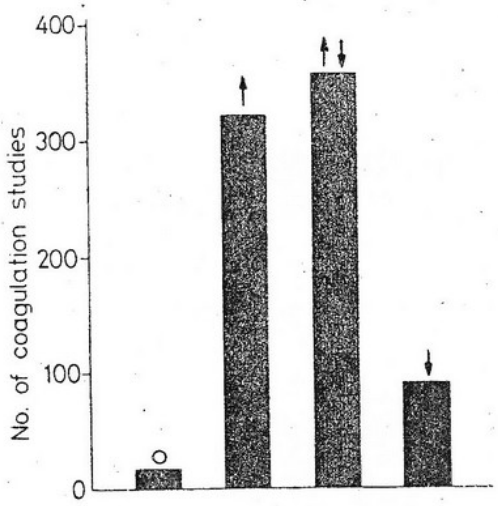

Fig. 1. Results of coagulation studies in glomerulonephritis and in the nephrotic syndrome. ○ = normal coagulability, ↑ = hypercoagulability, ↓ = hypocoagulability

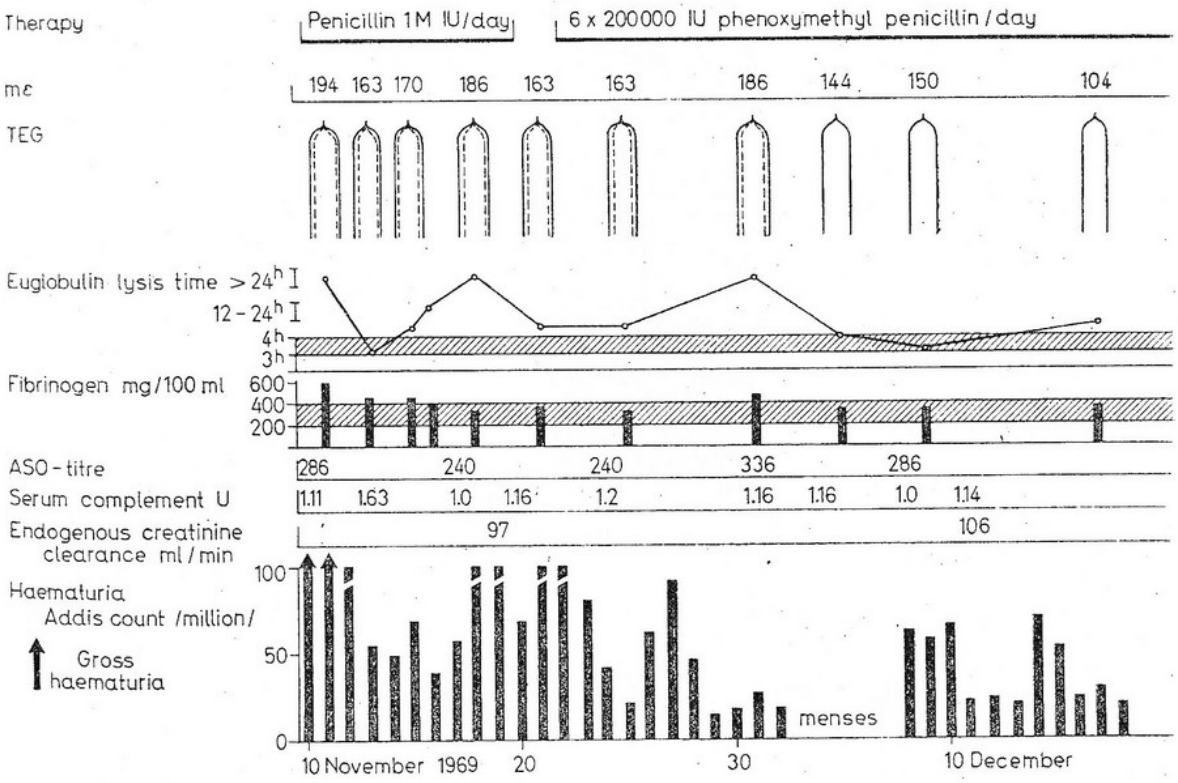

Fig. 2. Coagulation defects at the onset of acute glomerulonephritis

as endogenous creatinine clearance pointed to a normal glomerular function. At this stage, fibrinolytic activity was still reduced. This phenomenon which was observed in several similar cases may be regarded as a residual coagulation defect (Fig. 2). The opposite phenomenon, an enhanced fibrinolytic activity of plasma, may occur occasionally as a sign of a residual coagulation defect. In some very mild cases the fibrinolytic activity of plasma may be

increased early according to euglobulin lysis time, or any changes in coagulation may be absent.

Acute exacerbations of chronic glomerulonephritis are also accompanied by hypercoagulability.

The patient, a 27-year-old male had been under our care for years for chronic inactive glomerulonephritis. Apart from minor signs of hypocoagula-

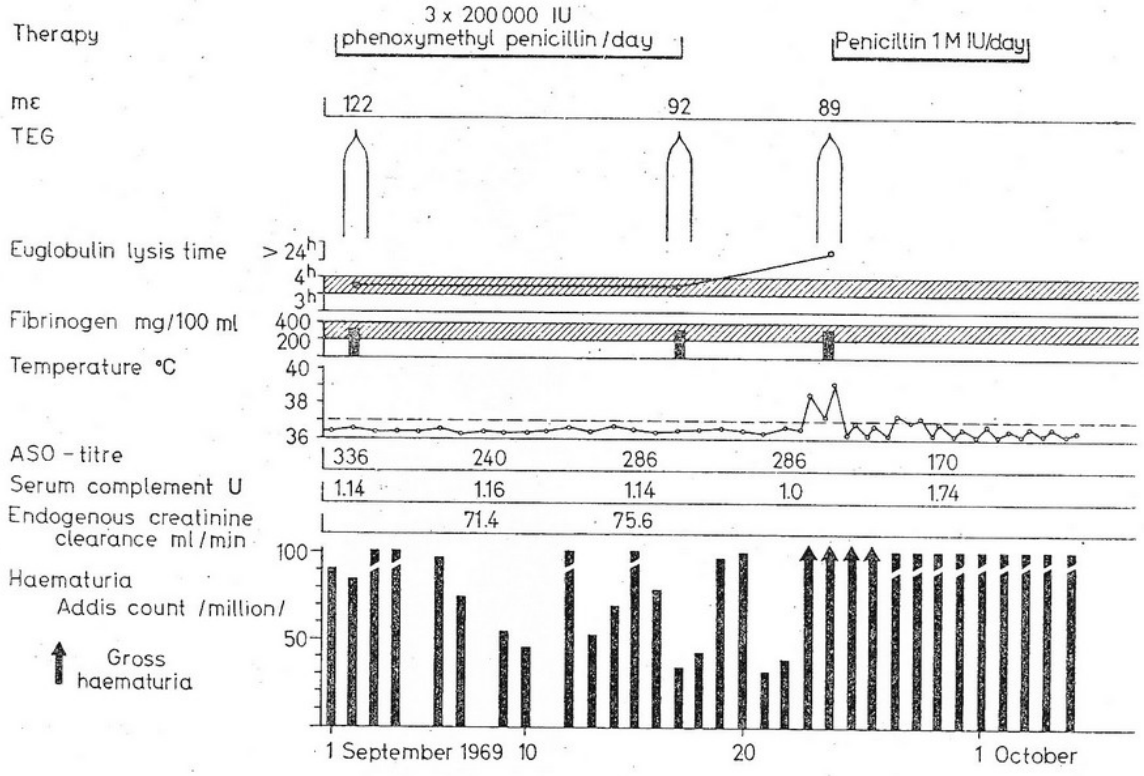

Fig. 3. Reduction in plasma fibrinolytic activity during acute exacerbation of chronic glomerulonephritis

bility no other clotting abnormality had been noted. He had been on a preventive scheme of oral penicillin which was discontinued on admission. A few days later he developed a sore throat with fever and gross haematuria. A pharyngeal swab yielded β-haemolytic streptococci. Here we were able to follow up the coagulation defect associated with an acute exacerbation from its earliest stage and thus to demonstrate a protracted euglobulin lysis time, i.e. a distinct reduction in fibrinolytic activity, within a few hours of the acute events. Thus, the earliest stage of blood coagulation disorders associated with the allergic process is an enhanced coagulability (Fig. 3).

The most conspicuous signs of hypercoagulability were found in the nephrotic syndrome, regardless whether the process was of the primary type or secondary to amyloidosis, diabetic glomerulosclerosis, systemic lupus erythe-

matosus, etc. On the evidence of our observations, hypercoagulability may be regarded as a sign of activity of the nephrotic syndrome.

One of the patients, a 28-year-old female, was admitted with a primary nephrotic syndrome. Administration of furosemide (Lasix, Hoechst, Frankfurt) induced a spectacular improvement, with the loss of 15 litres of oedema fluid in three weeks, as well as an increase in serum protein concen-

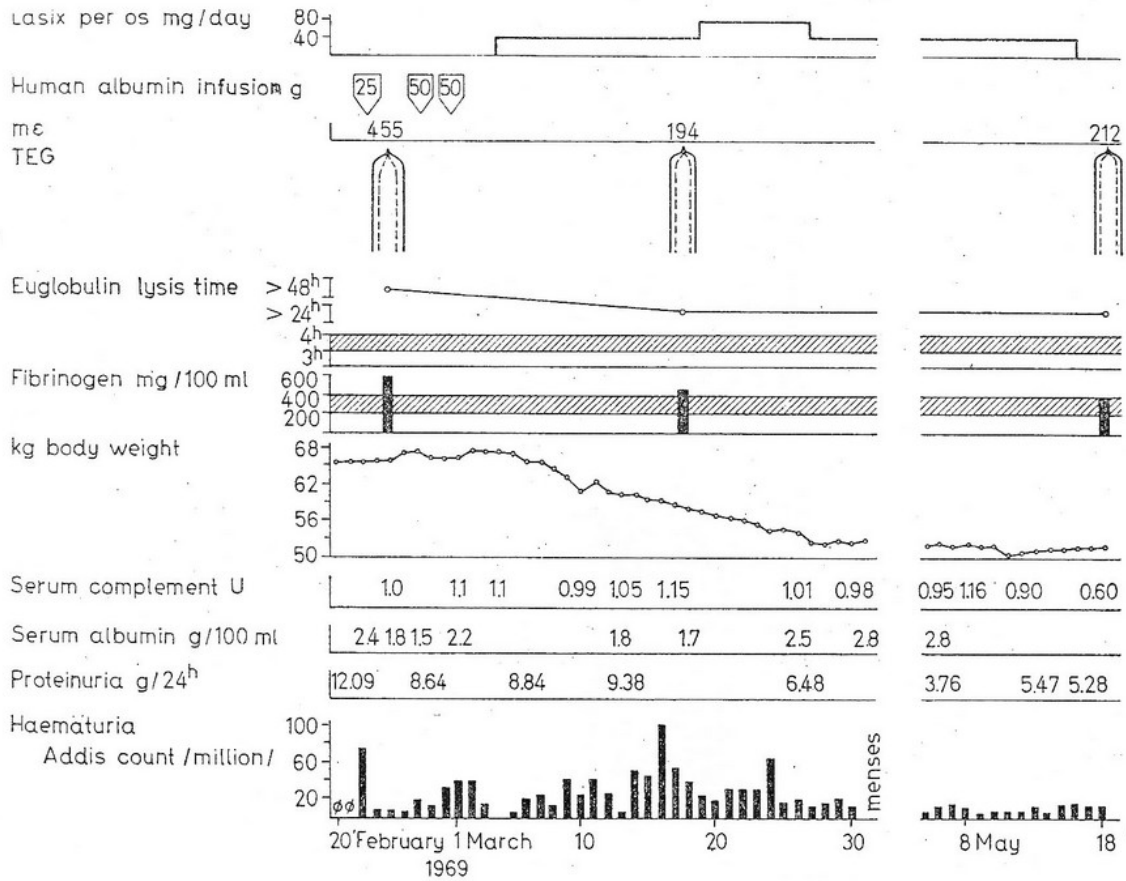

Fig. 4. Coagulation defects in primary nephrotic syndrome

tration and a fall of daily urinary protein excretion from 12 g to 3 or 5 g. However, blood clotting was still enhanced, as indicated by the thromboelastographic pattern and by the diminished spontaneous fibrinolysis. The serum complement titre was declining as a sign of immunological activity. Therapy had thus little influence on the coagulation defect, and in fact later an exacerbation ensued (Fig. 4).

Combination of symptomatic and immunosuppressive treatment may completely change the situation, as illustrated by the following case.

A 16-year-old male had been under observation for primary nephrotic syndrome, i.e. for "pure" nephrosis. An elevated plasma fibrinogen level, a reduced fibrinolytic activity together with a broad thromboelastogram had repeatedly been found prior to treatment. Administration of prednisolone

and subsequently of furosemide resulted in a loss of 20 litres of oedema fluid. Parallel with the clinical response hypercoagulability changed temporarily into hypocoagulability, as indicated by an abnormal narrowness of the thromboelastogram. The low serum complement level returned to normal and lasting remission ensued (Fig. 5).

The following case of amyloidosis represents the group where the nephrotic syndrome was elicited by some identifiable primary process.

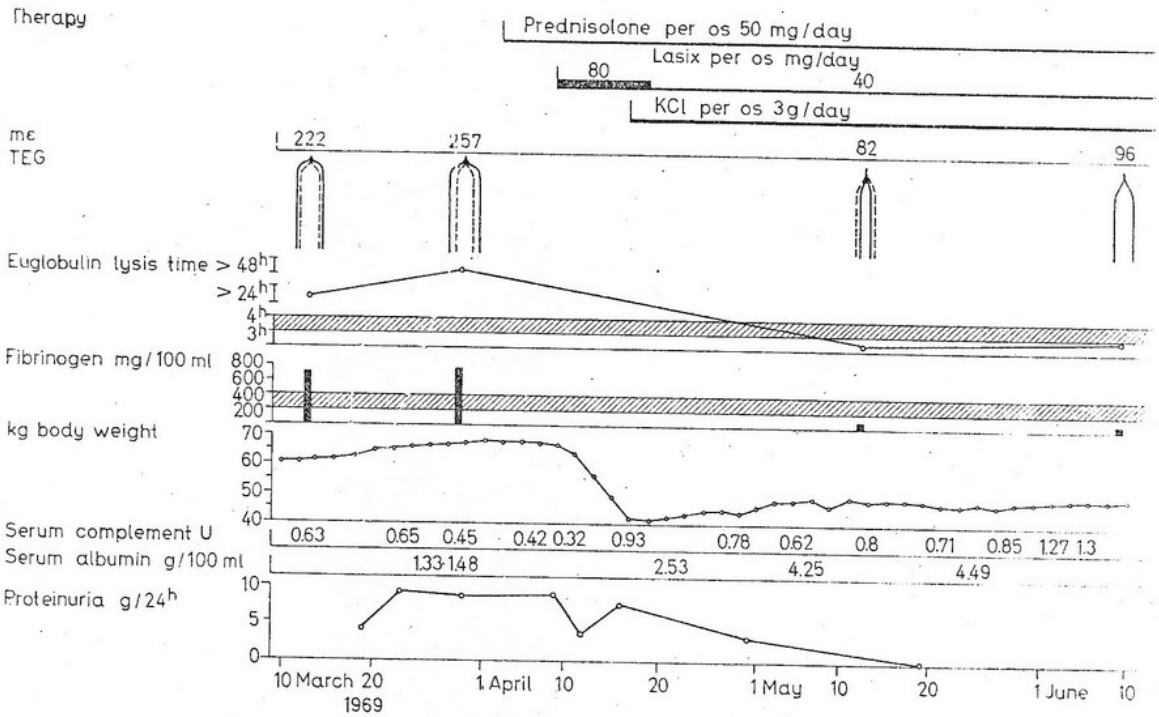

Fig. 5. Coagulation defects in primary nephrotic syndrome ("pure" nephrosis)

The patient was a 59-year-old female with clotting disturbances which had been investigated for the last months without showing any change. She was started on anticoagulant therapy. To acenocoumarol (Syncumar, EGYT, Budapest), the thromboelastogram showed a typical response. However, thus far we cannot yet assess the effect of anticoagulants in amyloid nephrosis, though persistent hypercoagulability belongs to the typical features of amyloidosis (Fig. 6).

One of the cases provided us with the opportunity of studying the coagulation disorders associated with Goodpasture's syndrome. The patient was a 19-year-old female. Fig. 7 sums up the results of investigations and the clinical features. The clinical course was marked by hypercoagulability as reflected by hyperfibrinogenaemia and an excessive reduction, if not an entire lack, of fibrinolytic activity and an abnormally broad thromboelastogram. The results have been represented diagrammatically according to GERENDÁS [9].

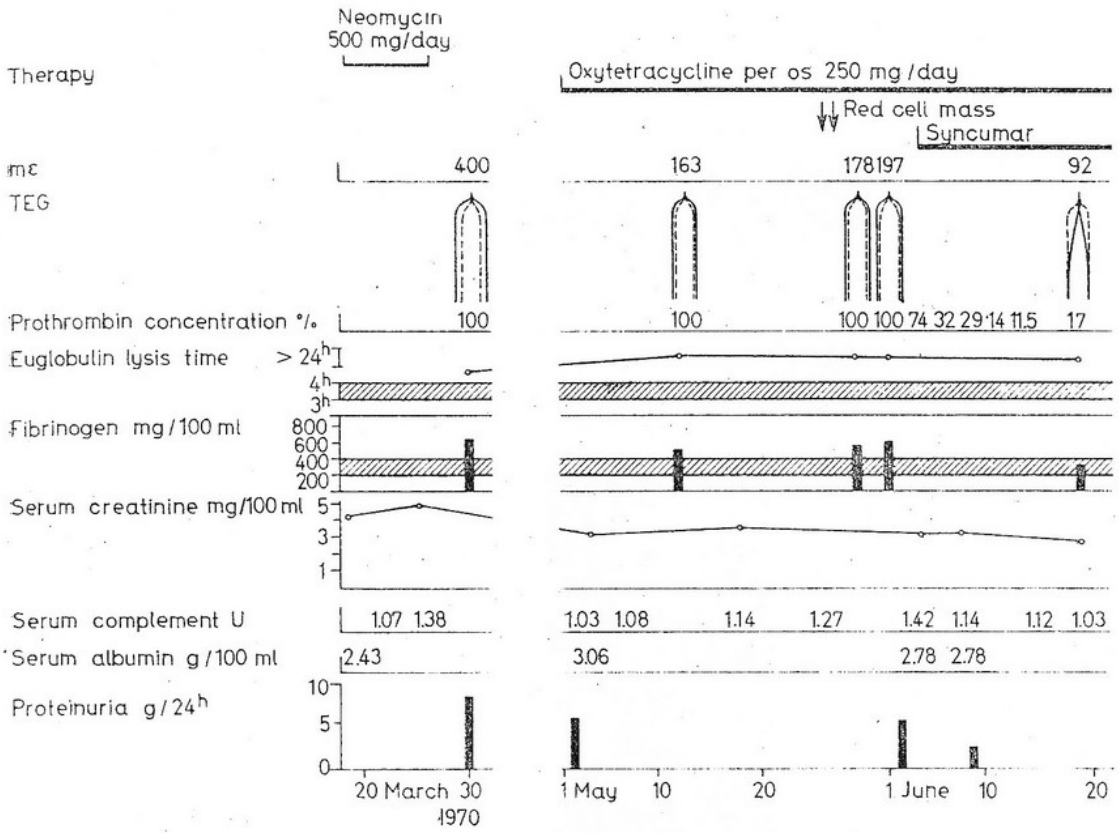

Fig. 6. **Persistent hypercoagulability in renal amyloidosis**

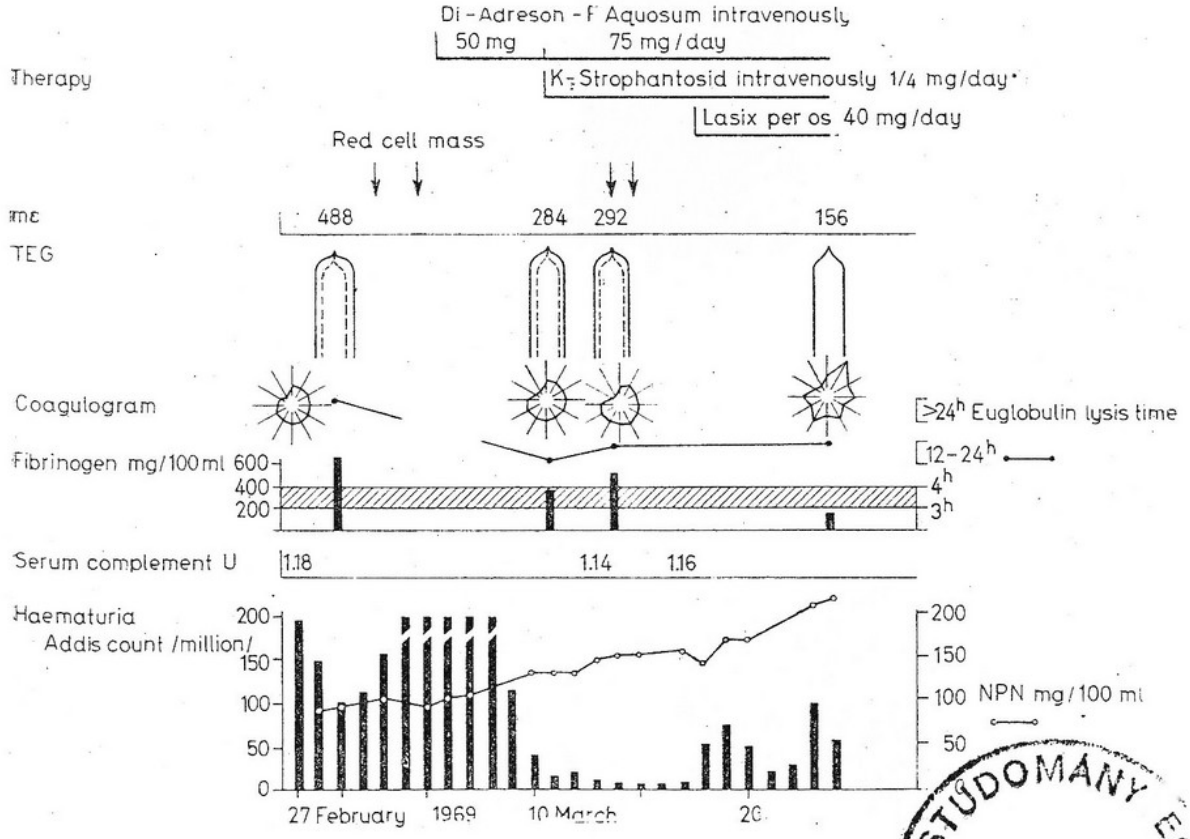

Fig. 7. Coagulation defects in Goodpasture's syndrome

On the evidence of the coagulogram performed before death the patient developed a bleeding tendency terminally, most probably under the influence of an antithrombin factor of heparin character. We have connected this finding with the terminal events. The suction cup test and the tourniquet test revealed an excessive capillary fragility. There is immunological evidence that Goodpasture's syndrome involves the formation of antibodies directed against the basement membrane, thus linking up the renal and pulmonary alterations with an autoimmune pathomechanism [2, 15]. On confronting these results with our findings it appears that the bleeding tendency in Goodpasture's syndrome is connected with an abnormal capillary permeability.

As to the hypocoagulability in this case, it is by no means an unfavourable sign as regards the activity of nephritis or nephrosis; it was usually observed in inactive chronic nephritis or after successful immunosuppressive treatment, as seen in Fig. 5.

Discussion

Hypercoagulability is a sign of activity of glomerulonephritis and nephrosis, particularly informative in the nephrotic syndrome. One of our patients had developed signs of hypercoagulability quite suddenly and went into a relapse soon afterward. In other words, the recurrence had been foreshadowed by an increase in blood coagulability, and this would call for the inclusion of coagulation tests into the follow up scheme in renal disease.

Persistent hypercoagulability is an unfavourable prognostic sign. We have lost 11 patients with glomerulonephritis or nephrosis in the last years. Hypercoagulability was confirmed by an increased plasma fibrinogen level, a reduced fibrinolysis, and a typical thromboelastogram in 9 patients and by two of these signs in 2 patients. On the other hand, hypocoagulability points to a favourable prognosis, as it did in fact in our cases of chronic glomerulonephritis of stationary nature.

These observations have their implications in the intriguing problem of the anticoagulant treatment of glomerulonephritis [11, 13]. Recently, BERLYNE and MALLICK [3] have suggested that ischaemic heart disease was one of the complications of the nephrotic syndrome, with an incidence 85 times as high as in the age-matched general population. We have also observed coronary occlusion in primary nephrotic syndrome. Two of our patients with Schoenlein—Henoch's purpura associated with glomerulonephritis developed digital gangrene; one of these patients died, the other had amputations of several digits.

These observations have prompted us to use anticoagulants in the diseases under discussion. However, in the 8 cases of glomerulonephritis or nephro-

sis where it had been employed, it failed to produce any improvement, though the clinical course of two patients certainly encourage further attempts. One of them, a male with systemic lupus erythematosus, developed vein thrombosis of right leg. He had been in a preuraemic condition when started on acenocoumarol. This treatment was continued for 18 months, until death. At necropsy, both renal veins, particularly the right one, were narrowed by organizing thrombi. The inference that without anticoagulant therapy occlusion of both renal veins would have inevitably ensued, almost suggested itself. In the other case, a patient with primary nephrotic syndrome, leg vein thrombosis recurred four times before anticoagulant therapy had been prescribed. Since two years he had no recurrence. Although the data in the literature are scarce [14] and our observations still too few to be conclusive, nevertheless, they point to the advantage of combined anticoagulant and corticosteroid or cytostatic treatment.

Finally, the question arises whether glomerulonephritis and the nephrotic syndrome are to be regarded as coagulopathies? This must be answered in the negative, since the coagulation defects fail to account for the entire syndrome, though they certainly do belong to it, in the same manner as oedema, hypertension or haematuria belong to the clinical pattern of glomerulonephritis.

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